Ventolin HFA Dossier

This information is provided in response to your request for information about Ventolin® HFA (albuterol sulfate) Inhalation Aerosol.

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Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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1. Change Summary

- **Section 4.2 Dosage Forms, Package Sizes, NDC, WAC Cost per Unit Table 1 (February 2009) —** Updated WAC prices
- **Section 7 Spray Force Comparison (February 2009) —** Added this section with data comparing the spray force of Ventolin HFA to generic albuterol CFC, Proventil HFA and ProAir HFA.
- **Appendix Table 2 (February 2009) —** Added new indication for ProAir HFA (children 4 years of age and older)
- **Appendix Table 2 (February 2009) —** Added 60 inhalation size of Ventolin HFA

2. EXECUTIVE SUMMARY

NAEPP Guidelines for the Management of Asthma

Inhaled short-acting beta$_2$-agonists, such as albuterol, are the drug of choice for treating acute asthma symptoms or exacerbations and for preventing episodes of exercise-induced bronchospasm.(1) Regularly scheduled, daily use of short-acting beta$_2$-agonists for the treatment of asthma is not recommended.

Monitoring Contents of Metered-Dose Inhaler

In a random telephone interview of 500 families with asthma in the U.S, 25% (87/342) of respondents receiving bronchodilator therapy found their metered-dose inhaler empty during an asthma exacerbation.(2) Of those, 82% considered their metered-dose inhaler empty when the canister was completely exhausted. Results from the survey demonstrated a lack of reliable means for monitoring the contents of metered-dose inhalers. As a result, patients may be at risk for inadequately managing their asthma or an asthma exacerbation. Additionally, patients may be refilling their inhaler more frequently than required. Manually tracking the number of actuations is often impractical when a rescue inhaler is used on an irregular basis. Metered-dose inhalers which include a dose counting feature may help eliminate uncertainty about the number of doses remaining in the inhaler.

Benefits of Ventolin HFA

• *Ventolin HFA* contains albuterol, a potent short-acting beta$_2$-agonist bronchodilator, and a hydrofluoroalkane (HFA) propellant. *Ventolin HFA* does not contain chlorofluorocarbons (CFCs).

• *Ventolin HFA* is supplied with a dose counter physically attached to the canister to show the number of doses remaining in the canister. The dose counter begins at 204, which allows for 4 priming sprays, and counts down to 000.

• The spray characteristics of *Ventolin HFA* were compared with those from a generic albuterol chlorofluorocarbon (CFC) formulation (Armstrong), with Proventil® HFA (Schering Plough) and with ProAir® HFA (Teva). *Ventolin HFA* had the highest mean maximum plume impact force followed by generic albuterol CFC (58.8 vs 42.2 mN). The spray duration and mean maximum temperature drop 6 mm from the mouthpiece were also similar for *Ventolin HFA* and generic albuterol CFC.

• *Ventolin HFA* has a fast onset of action. One study in adults and adolescents found the mean time to onset (defined as a 15% increase in forced expiratory volume in one second [FEV_1] over pretreatment values) was 5.4 minutes, the mean time to peak effect was 56 minutes, and the mean duration of effect was 4 hours. (3)

• *Ventolin HFA* is approved for use in children $\geq$ 4 years of age. (3)

Efficacy

• A 12-week, randomized, double-blind study compared *Ventolin HFA*, *Ventolin* CFC (no longer available), and placebo in approximately 300 adults and adolescents with mild to moderate asthma. *Ventolin HFA* produced a significantly greater improvement in FEV_1 over pretreatment values than placebo, but was similar in efficacy to *Ventolin* CFC.(3)

• Another 12-week, randomized, double-blind study evaluated the safety and efficacy of switching from *Ventolin* CFC to *Ventolin HFA* in approximately 300 adults and adolescents with mild to moderate asthma. A third of the patients switched from *Ventolin* CFC to *Ventolin HFA*, a third switched to placebo and the rest continued receiving *Ventolin* CFC. Serial FEV_1 measurements found that *Ventolin HFA* resulted in significant improvements in lung function compared to placebo. Furthermore, switching from *Ventolin* CFC to *Ventolin HFA* did not result in any clinically significant changes in efficacy. (3) (4)

• A 2-week, randomized, double-blind study compared *Ventolin HFA*, *Ventolin* CFC and placebo in 135 pediatric patients (4 – 11 years old) with mild to moderate asthma. Serial pulmonary function tests found that *Ventolin HFA* resulted in significantly greater improvements in pulmonary function compared to placebo, but there was no significant difference between *Ventolin HFA* and *Ventolin* CFC.(3) (5)

Safety

• Adverse events in adults and adolescents (n=202) treated with *Ventolin HFA* for 12 weeks with an incidence ≥3% and occurring more frequently than in the placebo group included: throat irritation 10%, upper respiratory inflammation 5%, viral respiratory infections 7%, cough 5%, and musculoskeletal pain 5%. (3)

• *Ventolin HFA* can produce paradoxical bronchospasm, which may be life threatening. Paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister. (3)

• *Ventolin HFA* can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Such effects are uncommon after administration of *Ventolin HFA* at recommended doses, but if they occur the drug may need to be discontinued. Beta-agonists have also been reported to produce electrocardiogram changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, *Ventolin HFA* should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.(3)

• If the patient needs more doses of *Ventolin HFA* than usual, this may be a marker of asthma destabilization. This requires reevaluation of the patient and treatment regimen giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. (3)

• Do not exceed the recommended dose of *Ventolin HFA*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. (3)

• *Ventolin HFA* alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen. (3)

• Immediate hypersensitivity reactions may occur after administration of *Ventolin HFA* as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. (3)

Indications

Ventolin HFA is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease.(3) *Ventolin HFA* is also indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Dosing

Asthma in Adults and Children (≥ 4 years old)

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is 2 inhalations (180 mcg albuterol base) repeated every 4 to 6 hours.(3) In some patients, 1 inhalation every 4 hours may be sufficient.

Prevention of Exercise-Induced Bronchospasm in Adults and Children (≥ 4 years old)

The usual dosage is 2 inhalations (180 mcg albuterol base) 15 to 30 minutes before exercise.(3)

3. DISEASE DESCRIPTION

3.1 Asthma

Asthma: Epidemiology and Risk Factors

Asthma is one of the most common chronic diseases in the United States. According to the American Lung Association's Trends in Asthma Morbidity and Mortality report, approximately 22.9 million Americans (6.8 million children) had asthma in 2006.(6) In addition, 12.4 million people, or 54% of the people who had asthma at the time of the survey, had experienced an asthma attack in the previous year. Health care use in 2005 included 488,594 asthma-related hospitalizations and approximately 1.8 million emergency department visits. Deaths from asthma in 2005 numbered 3,884.(7) The economic cost of asthma in 2005 was estimated at $19.7 billion.(6)

Atopy, the genetic susceptibility for the development of an IgE-mediated response to environmental allergens, is the strongest identifiable predisposing factor for developing asthma.[1]

Asthma: Pathophysiology

Asthma is a chronic disease of bronchoconstriction, inflammation and remodeling of the airways.[1] In asthma, airway narrowing and subsequent airflow limitation lead to the symptoms of asthma. In an acute exacerbation, contraction of the bronchial smooth muscle, or bronchoconstriction, occurs in response to exposure to an inhaled allergen or irritant. The inflammatory reaction to an inhaled allergen involves a complex interaction of a variety of cells, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, smooth muscle cells, and epithelial cells. As inflammation becomes more progressive and the disease becomes more persistent, factors such as edema, inflammation, mucus hypersecretion, and hypertrophy and hyperplasia of the airway smooth muscle lead to further airflow obstruction. In addition, airway inflammation results in an increase in the existing airway hyperresponsiveness. Over time, permanent structural changes may occur which result in loss of lung function that may be only partially reversible with therapy, also known as airway remodeling. Some of the structural changes which may occur include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and secretion. The interaction between symptoms, airway obstruction, bronchial hyperresponsiveness, and inflammation determines the clinical manifestations and severity of asthma as well as the response to treatment.

Asthma: Clinical Presentation

Patients with asthma have recurrent episodes of cough (particularly worse at night), wheezing, difficulty breathing, and chest tightness.[1] These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Patients also experience bronchial hyperresponsiveness to various triggers. On physical examination, patients may exhibit hyperexpansion of the thorax (especially in children), use of accessory muscles, hunched shoulders, and chest deformity. Wheezing may occur during normal breathing or during a prolonged phase of forced exhalation, although wheezing may be absent between exacerbations. Patients may have increased nasal secretion, mucosal swelling and nasal polyps. In addition, atopic dermatitis/eczema or any other allergic skin condition may be present. Symptoms may be absent during the time of examination; therefore, a history of symptoms is important.

Asthma: National Asthma Education and Prevention Program Guidelines

The 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommend to first assess severity in newly diagnosed patients to determine initial therapy for patients with asthma.[1] For patients who have been receiving long-term controller medications, the guidelines recommend regular assessments of asthma control for monitoring and adjusting therapy. The guidelines provide impairment and risk criteria to assess both asthma severity and asthma control for each of the three age ranges: 0-4 years of age, 5-11 years of age, and ≥12 years of age. Impairment is defined as the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced. Risk is defined as the likelihood of either asthma exacerbations, progressive decline in lung function, or risk of adverse effects from a medication. In addition, the guidelines also recognize the use of validated assessment tools, like the Asthma Control Test and Childhood Asthma Control Test, to assess asthma control.

For each age range, there are six treatment steps which provide preferred, and for some steps alternative, treatment recommendations for both intermittent and persistent types of asthma. All patients, regardless if they have intermittent or persistent asthma, should receive a short-acting $beta_2$-agonist for quick relief of their asthma symptoms. Inhaled corticosteroids, either alone or in combination with other controller medications, continue to be the preferred first-line therapy for children and adults with persistent asthma. The guidelines also recommend the use of a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) as a preferred therapy for patients ≥5 years of age whose asthma is uncontrolled on their current controller and for patients ≥12 years of age with moderate to severe persistent asthma who are new to controller therapy.

3.2 Exercise-induced Bronchospasm (EIB)

EIB: Definition and Epidemiology

Exercise-induced bronchospasm (EIB) or exercise-induced asthma (EIA) is defined as a transient increase in airway resistance resulting from participation in strenuous physical activity. [8] In terms of lung function, EIB is characterized by a decrease in forced expiratory volume in 1 second (FEV_1) by at least ten percent. The prevalence of EIB varies from approximately 5% to 20% in the general population and 30% to 70% among elite athletes. [9] In patients with persistent asthma, the prevalence is at least 90%. Among sufferers of allergic rhinitis, the prevalence is estimated to be about 40%. [8]

EIB: Pathophysiology

EIB is a bronchospastic event caused by loss of heat, water, or both from the lungs during exercise because of hyperventilation of air that is cooler and dryer than that of the respiratory tree. [1] Some studies also suggest that the release of inflammatory mediators may be involved in the etiology of EIB.

EIB: Clinical Presentation

Asthma attacks precipitated by exercise are no different than attacks brought on by other stimuli. Patients experience wheezing, coughing, dyspnea, and chest tightness, in conjunction with airflow limitation and hyperinflation. Because children and young adults engage in more frequent physical activity, EIB is more commonly seen in these age groups. In EIB, the airways undergo dilation during physical activity which is followed by increasing obstruction beginning once the physical activity stops. Patients will show signs of airway obstruction within five to ten minutes after strenuous physical activity, which in most cases, reverses after twenty to thirty minutes. There are many factors which influence the severity of an attack including a patient's baseline airway reactivity, level of physical activity, and climate.

EIB: Approaches to Treatment

The most appropriate treatment for EIB is prophylaxis. Asthmatic patients can lessen the severity of attacks by engaging in a warm-up period prior to physical activity. Pharmacologic therapy depends upon the presentation of the disease. If EIB is present in an otherwise asymptomatic patient, there is no need for regularly scheduled medications. However, these patients should be monitored regularly to ensure they have no symptoms of asthma or reductions in peak expiratory flow in the absence of exercise because EIB is often a marker of inadequate asthma control. [1] Treatment of choice in a patient with EIB only consists of inhalation therapy with beta-agonists as needed immediately prior to physical activity. Cromolyn, nedocromil or leukotriene modifiers may also be useful for some patients.

If EIB is only one part of the asthmatic symptomatology, daily pharmacologic therapy is warranted. These patients require anti-inflammatory and bronchodilating medications to help control acute asthmatic symptoms.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

Generic Name: albuterol sulfate HFA inhalation aerosol

Brand Name:: Ventolin® HFA

Therapeutic Class: Short-acting $beta_2$-adrenergic bronchodilator for inhalation

4.2 Dosage Forms, Package Sizes, NDC, WAC Cost per Unit

Table 1. Product Strength, Description, Package Size, NDC, and WAC

Strength	Description	Package Size	NDC	WAC
Albuterol sulfate 120 mcg equivalent to albuterol (base) 90 mcg from the mouthpiece	Pressurized aluminum canister fitted with a dose counter, a blue plastic actuator and a blue strapcap. Product is packaged in a moisture-protective foil pouch with desiccant.	Each canister contains 200 inhalations	0173-0682-20	$30.10*
Albuterol sulfate 120 mcg equivalent to albuterol (base) 90 mcg from the mouthpiece	Pressurized aluminum canister fitted with a dose counter, a blue plastic actuator and a blue strapcap. Product is packaged in a moisture-protective foil pouch with desiccant.	Each canister contains 60 inhalations	0173-0682-24	$15.00†
WAC=wholesale acquisition cost. WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge-backs. * Cost effective as of June 16, 2006. † Cost effective as of July 1, 2008. Store between 15° and 25°C (59° and 77°F). The inhaler should be discarded when the counter reads 000 or 6 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister in water to determine the amount of drug remaining in the canister.				

4.3 AHFS or Other Drug Classification

AHFS Drug Classification: 12:12.08.08 Selective β_2-adrenergic agonists

4.4 FDA Approved Indications

FDA Approval Date for *Ventolin HFA*: April 2001

FDA Approved Indications: *Ventolin HFA* is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease. *Ventolin HFA* is also indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.6 Pharmacology

Refer to Enclosed Prescribing Information.

4.7 Pharmacokinetics/Pharmacodynamics

Refer to Enclosed Prescribing Information.

4.8 Contraindications

Refer to Enclosed Prescribing Information.

4.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

Refer to Enclosed Prescribing Information.

4.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

4.15 Product Comparison

Table 2. - See Appendix

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED INDICATIONS)

5.1 Adult and Adolescent Asthma and EIB Trials

CLINICAL INFORMATION

Single-Dose Asthma Studies

The effects of albuterol CFC, albuterol HFA, and placebo HFA were evaluated in 63 adolescent and adult patients with asthma [mean forced expiratory volume (FEV_1) 69.2% of predicted].[10] In this randomized, double-blind, crossover study, lung function response was measured over six hours after the single-dose administration. The effect of both active drug formulations on the area under the time versus concentration curve (AUC) FEV_1 and peak effect (percent of baseline FEV_1) was similar with no statistically significant difference between equivalent doses (Table 3). No differences in adverse effects were noted.

Table 3. Lung Function Response Following Single-dose Administration [10]

	Placebo HFA	Albuterol HFA 100mcg	Albuterol HFA 200mcg	Albuterol HFA 400mcg	Albuterol CFC 100mcg	Albuterol CFC 200mcg
AUC FEV_1(L·hr)	0.24	1.27	1.69	1.97	1.5	1.77
FEV_1 (L)	1.09	1.04	1.23	1.21	1.29	1.14
Peak effect (% of baseline FEV_1)	108.8	119.9	123.2	125.5	121.2	123
AUC = area under the time versus concentration curve, FEV_1 = forced expiratory volume in one second						

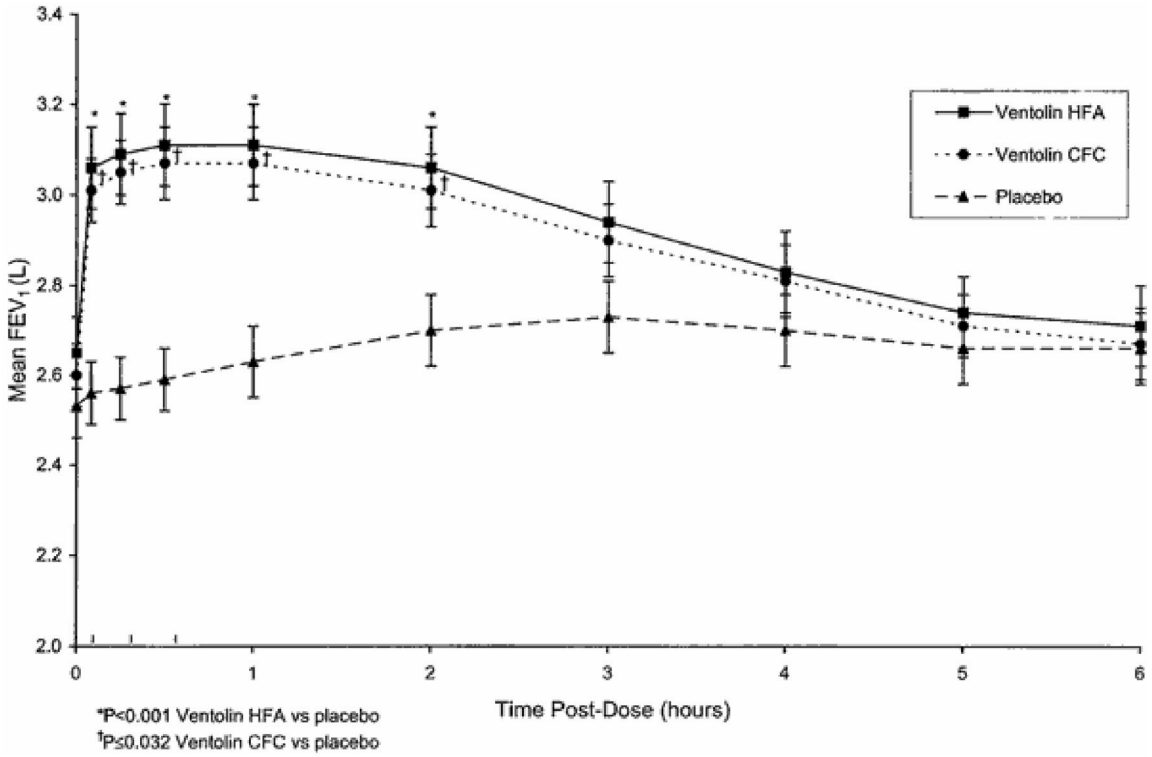
In a preliminary report, albuterol CFC, albuterol HFA, and placebo HFA were compared via a crossover, single-blind study.[11] Twenty-four patients with asthma (mean FEV_1 65% of predicted) received a single 120 mcg dose (ex-valve) of each treatment. Each patient received escalating doses (1 puff, 2 puffs, four puffs, and eight puffs) at 30 minute intervals with a 1-8 day washout period between study days. Heart rate, FEV_1, and serum potassium were measured at baseline and 12, 16, and 18 minutes after each dose. Albuterol CFC and HFA yielded similar bronchodilatory effects, which were significantly greater than the placebo HFA effect ($P < 0.05$). The 90% confidence intervals for mean FEV_1 increase between albuterol CFC and HFA were within ±0.1L at all cumulative inhalations. Both active treatments were well tolerated with the only significant differences from placebo for heart rate and serum potassium occurring with the highest cumulative dose.

Multiple Dose Asthma Studies

In a preliminary abstract, the safety of albuterol HFA was evaluated over 12 months in an open-label trial.[12] Adolescent and adult patients (N = 452) with asthma (mean FEV_1 80% of predicted) used albuterol HFA 180 mcg via MDI four times daily. The adverse event profile of albuterol HFA was similar to that of albuterol CFC. Bronchitis, headaches, and upper respiratory tract infections were the most common adverse events with headache being the only drug-related event that occurred in more than 1% of patients. No serious drug-related adverse events occurred. Three patients had clinically significant electrocardiographic abnormalities; however, medical intervention was not required. Overall, 70% of the subjects did not experience an asthma exacerbation during the study.

The comparative efficacy of albuterol HFA and albuterol CFC via MDI was explored in 313 patients (≥12 years of age) with asthma (mean FEV_1 67% of predicted).[4] All patients in this double-blind study received albuterol CFC for three weeks prior to being randomized to either albuterol CFC 180 mcg four times daily, albuterol HFA 180 mcg four times daily, or placebo HFA four times daily for 12 weeks. The FEV_1 was measured at baseline (run-in day 14), treatment day 1, week 6 and week 12 before the dose, 5, 15, and 30 minutes after the dose, and hourly up to six hours after the dose. Lung function remained stable over the 12 weeks for all patients (predose FEV_1 68% - 74%). The morning peak expiratory flow (PEF), evening PEF, daily asthma symptom score, and nighttime awakenings were similar during albuterol CFC and HFA administration. The mean FEV_1 response is shown in Figure 1. Asthma exacerbations occurred in 4% of the albuterol HFA group, 5% in the albuterol CFC group, and in 8% of the placebo HFA group. Adverse effects were similar between the CFC and HFA albuterol formulations with upper respiratory tract infection, headache, and throat irritation being the most commonly reported. No clinically significant cardiovascular effects were observed.

Figure 1. Mean FEV_1 Response after 12 Weeks of Treatment [4]



Similar results were found in another 12-week comparative study of albuterol CFC and HFA formulations in 547 adolescent and adult patients with asthma (mean FEV_1 2.44 L to 2.51 L).[13] All patients received 4 weeks of albuterol CFC 200 mcg 4 times daily via a MDI before being randomized to albuterol HFA or CFC 200 mcg 4 times daily. At the end of 12 weeks, all patients again received 4 weeks of albuterol CFC 200 mcg 4 times daily. The primary outcome variable was a change in heart rate. Albuterol CFC and HFA demonstrated similar efficacy and safety. The mean heart rate change was 1 and 2 beats per minute for the CFC and HFA formulations, respectively. A slight reduction in serum potassium values was seen with the HFA (-0.08 mmol/L) and CFC (-0.07 mmol/L) formulations. No significant differences for FEV_1 and PEF were observed between the albuterol CFC or HFA groups (Table 4). No serious adverse events were judged related to the study medications. Twelve patients found the HFA product to have an unpleasant taste compared with four patients with the CFC product.

Table 4. Mean FEV_1 and PEF Values [13]

		HFA	CFC
FEV_1 (L)	Baseline	2.51	2.44
	Week 12	2.49	2.47
	Run-out week 1	2.54	2.49
	Run-out week 4	2.56	2.51
PEF (L/min)	Baseline	406	404
	Week 12	397	405
	Run-out week 1	401	406
	Run-out week 4	409	407
FEV_1 =forced expiratory volume in one second, PEF=peak expiratory flow			

The efficacy and safety of rescue albuterol CFC and HFA were assessed in a double-blind, parallel-group study. [14] Adult patients (N = 423) with mild to moderate asthma (FEV_1 50% - 99% of predicted) who used between 2-12 puffs of albuterol every two days were randomized to receive as-needed albuterol 100 mcg CFC or HFA via MDI for four weeks. The median daily albuterol use (4 puffs) remained unchanged from the run-in period through the treatment period for both treatment groups. Additionally, the mean AM PEF, PM PEF, asthma symptom scores, and asthma exacerbation rates were similar for both treatment groups. Both albuterol formulations were well tolerated with 6% of patients in each group judged to have a drug-related adverse event (ear, nose, or throat disorders, malaise, pyrexia). One patient who received albuterol HFA experienced an unpleasant taste.

Exercise Induced Bronchospasm (EIB)

The efficacy of albuterol HFA for the prevention of EIB was determined in a single-dose study. [15] Patients (N = 18) ages 11-37 years with known EIB were subjected to submaximal exercise on a treadmill in a cool chamber. Lung function testing was done before exercise and 3, 5, 15, and 30 minutes after exercise. Patients repeated the exercise testing at least six hours after the first session and after inhalation of two puffs of albuterol HFA. The mean FEV_1 was significantly greater after exercise with albuterol HFA as compared to no pre-treatment (3.66L and 3.26L, respectively, $P < 0.01$). No adverse effects of albuterol HFA were noted.

The efficacy of albuterol HFA was compared to placebo HFA and albuterol CFC in a single-dose, double-blind, crossover study.[16] Adult patients (N=24) with known EIB and a mean FEV_1 65% of predicted were randomized to receive a single dose of albuterol 200 mcg CFC, albuterol 200 mcg HFA, or placebo HFA thirty minutes prior to a 6-minute submaximal treadmill exercise challenge. Vital signs and FEV_1 were recorded before exercise and up to 1 hour after exercise. Both albuterol formulations provided greater protection against exercise induced bronchoconstriction (see Table 5) and were associated with similar adverse events.

Table 5. Mean Maximal Percent Fall in FEV_1 After Exercise [16]

Albuterol HFA	Albuterol CFC	Placebo HFA
15.4%*	14.9%*	33.7%
*$P < 0.001$ versus placebo HFA		

5.2 Pediatric Asthma Trials

Children 2 to <4 years old

A double-blind, randomized, placebo-controlled study compared the safety and efficacy of *Ventolin HFA* to placebo in 77 children 2 to <4 years old with asthma symptoms (cough, wheeze, dyspnea, or chest tightness).[17,18] The children enrolled in this study had:

-a documented history of asthma symptoms

-experienced at least two episodes of increased asthma symptoms requiring medical attention

-asthma pharmacotherapy within the 12 months preceeding study initiation

-received maintenance asthma medication (other than systemic corticosteroids) and/or short-acting beta-agonists over the 4 weeks prior to study initiation.

After a 1-4 week run-in period, patients were randomized to *Ventolin HFA* 90 mcg three times daily, *Ventolin HFA* 180 mcg three times daily or placebo. Study medications were delivered using an Aerochamber Plus® or Optichamber® spacer with a facemask, with approximately half the study population using each type of spacer. Patients were allowed to continue other asthma medications if they were started at least 4 weeks prior to study initiation and the dose remained unchanged throughout the study. The primary endpoint was the mean change from baseline in the 24-hour asthma symptom score. Secondary endpoints included the mean percent change from baseline in daytime asthma symptom score, 24-hour rescue medication use, and percentage of symptom-free days.

At baseline, asthma symptom scores were mild and symptoms decreased slightly in all three groups over the 4 week study. There was no significant difference between the *Ventolin* and placebo groups, nor between the two *Ventolin* groups for the primary endpoint, mean change in 24-hour asthma symptom score from baseline to week four. Although patients treated with *Ventolin HFA* experienced fewer daytime asthma symptoms, a greater reduction in rescue medication use and more symptom free days than patients treated with placebo, the difference was not significant.

Adverse events are listed in Table 6. Mean values in systolic and diastolic blood pressure were similar at baseline and week 4. Similarily, mean values for heart rate, body temperature and respiratory rate at baseline were comparable to week 4 values.

Table 6. Study SBO20001 Number of Patients Experiencing Adverse Events [18]

	Placebo (N=26)	***Ventolin HFA* 90 mcg (N=26)**	***Ventolin HFA* 180 mcg (N=25)**
Pyrexia	2	2	1
Vomiting	2	1	1
Diarrhea	0	0	2
QT prolongation*	0	1	3
QTc prolongation*	0	1	0
Mild tremor†	1	3	2
*No patient had a QT or QTc interval greater than 460 msec †Tremor graded on 4 point scale from none to severe			

Infants to <2 years old

A multicenter, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of *Ventolin HFA* in children who ranged in age from birth to <2 years old.[19] Patients enrolled in this study had a history of wheezing, cough, dyspnea, or chest tightness with at least one episode of increased symptoms requiring medical attention and pharmacotherapy. Additionally, patients received daily maintenance asthma medication for at least 3 weeks prior to study entry and/or required a short-acting $beta_2$-agonist for relief of respiratory symptoms prior to study enrollment. Patients who met this criteria were randomized to *Ventolin HFA* 90 mcg three times daily, *Ventolin HFA* 180 mcg three times daily or placebo administered by an Aerochamber Plus® spacer with facemask for 4 weeks.

The primary efficacy endpoint was the mean change from baseline in 24-hour asthma symptom score. Secondary endpoints included rescue albuterol use, daytime asthma symptoms scores, and percentage of symptom free days.

There was no significant difference between the *Ventolin*vs placebo groups, or between the two *Ventolin* groups for the primary endpoint. Efficacy results were also similar across treatment groups for the secondary endpoints listed above.

Adverse events occurring in at least 3 patients per treatment group are listed in Table 7. The mean change in systolic blood pressure for patients treated with *Ventolin HFA* 90 mcg three times daily was slightly higher (5.5 mmHg) at week 4 compared to baseline. Week 4 mean diastolic blood pressure, heart rate, body temperature, and respiratory rate were comparable to baseline values for each of the three treatment groups. Baseline to week 4 mean changes in QT and QTc intervals were small and no individual had a QT or QTc interval >460 msec (Fridericia's formula).

Table 7. Study SBO30001 Number of Patients Experiencing Adverse Events [19]

	Placebo (N=28)	***Ventolin HFA* 90 mcg (N=29)**	***Ventolin HFA* 180 mcg (N=29)**
Nasopharyngitis	3	2	4
Upper respiratory tract infection	3	0	5
Nasal congestion	1	3	1
Teething	3	4	1
Pyrexia	3	2	7
Sinus tachycardia	2	2	5

6. COMPARATIVE CLINICAL DATA

6.1 Compared to Other Albuterol HFA Formulations

There have been no clinical studies comparing *Ventolin HFA* to other albuterol sulfate HFA formulations.

6.2 Compared to Levalbuterol HFA

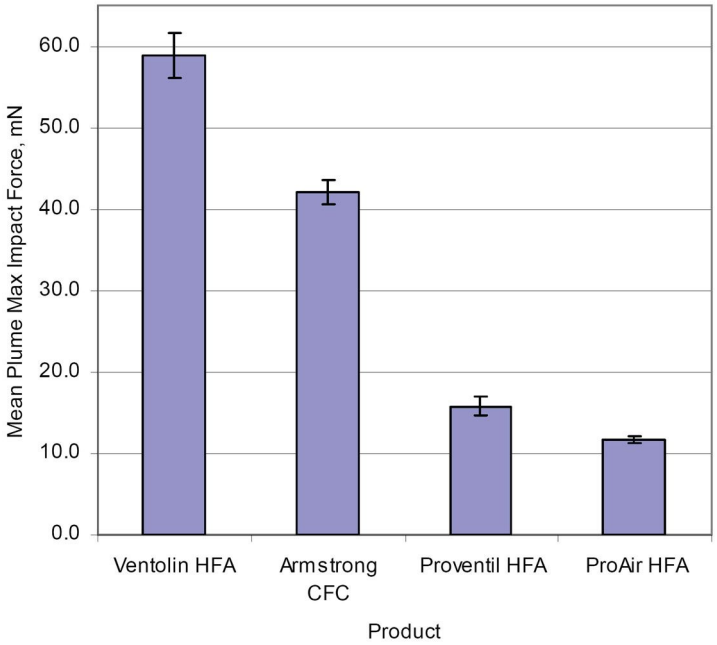
There have been no clinical studies comparing *Ventolin HFA* and levalbuterol HFA.

7. SPRAY FORCE COMPARISON

Spray characteristics

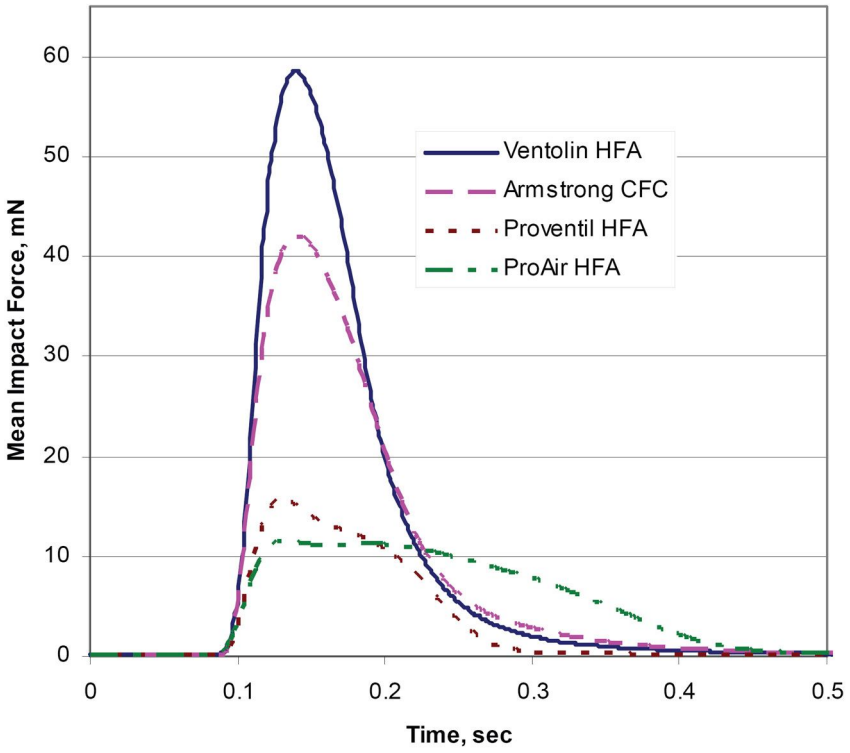
The spray characteristics of *Ventolin HFA* were compared with those from a generic albuterol CFC formulation (Armstrong) and with Proventil® HFA (Schering Plough) and ProAir® HFA (Teva). [20] After priming the metered-dose inhalers, plume force, spray duration, and plume temperature were determined using five inhalers for each product and three measurements from each inhaler (total of 15 evaluations for each product). *Ventolin HFA* had the highest mean maximum plume impact force at 58.8 mN followed by generic albuterol CFC (42.2 mN), Proventil HFA (15.8 mN) and ProAir HFA (11.7 mN). See Figure 2. The spray duration for *Ventolin HFA* was similar to generic albuterol CFC (see Figure 3). The mean maximum temperature drop 6 mm from the mouth piece was 30^{o}F, 33^{o}F, 10^{o}F, and 8^{o}F for *Ventolin HFA*, generic albuterol CFC, ProAir HFA, and Proventil HFA, respectively.

Figure 2. Mean Maximum Plume Impact Force



n = 5 inhalers x 3 measurement each for each product

Figure 3. Inhaler Force of Spray Impact



8. DOSE COUNTER INFORMATION

design characteristics

Ventolin HFA with dose counter (see Figure 4) is the same size and shape as *Ventolin HFA* without a dose counter, which is no longer commercially available. [21] [22] No extra steps are required to use or clean the metered-dose inhaler (MDI) and the counter increases the product weight by <5 grams. The force needed to actuate *Ventolin HFA* with counter is similar to that of *Ventolin HFA* without a dose counter (33 to 40 Newtons). *Ventolin HFA* is supplied with the counter physically attached to the canister, the joint is tamper evident, and the counter cannot be reset without permanent damage to the device (see Figure 5).

Figure 4. Rear View of *Ventolin HFA* MDI with Dose Counter

Figure 5. *Ventolin HFA* Canister with Dose Counter Attached

The dose counter begins at 204, allowing for 4 priming sprays, and counts down to 000. The inhaler should be primed before using it for the first time, when it has not been used for more than 2 weeks, or when it

has been dropped. [3] The MDI does not lockout additional actuations once the dose counter reaches 000. However, the correct amount of medication in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000 (after 200 actuations have been used) or 6 months after removal from the moisture protective foil pouch, whichever comes first. Never immerse the canister in water to determine the amount of drug remaining in the canister.

count accuracy

The accuracy of the dose counter was assessed after various test conditions to simulate normal use and patient misuse. [21] [22] The dose counter was 100% accurate after each test condition, except after dropping, in which 1 of 120 samples failed (99% accurate). The test conditions included:

• Weekly cleaning performed as described in the Patient Information leaflet

• Dropping 60 canisters and 60 canisters plus actuators 6-feet onto a hard surface. Half the samples were dropped in the valve side down position and the other half were dropped in the valve side up position. Note, one canister dropped valve side down was permanently damaged.

• Immersion in cold tap water for 10 minutes. Although the counter was 100% accurate, there was visible moisture inside the counter. The MDI with counter was not designed to be water resistant and the prescribing information for *Ventolin HFA* states that the metal canister should never be immersed in water.

• 50^{o}C for 24 hours

• -20^{o}C for 24 hours

• 25^{o}C/60% relative humidity for 12 months

• 30^{o}C/65% relative humidity for 12 months

• 40^{o}C/75% relative humidity for 12 months

• -20^{o}C/ambient relative humidity for 12 months

• 6 hour temperature cycle between -5^{o}C to 40^{o}C/ambient relative humidity for 12 months

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Appendix

Table 2. Comparison of Available Short-Acting Beta$_2$-Agonist Products

	Ventolin® HFA	**Proventil® HFA**	**ProAir® HFA**	**Xopenex HFA®**
Ingredients				
Active	albuterol sulfate	albuterol sulfate	albuterol sulfate	levalbuterol tartrate
Inactive	HFA	HFA, ethanol, oleic acid	HFA, ethanol	HFA, dehydrated alcohol, oleic acid
Formulation	Suspension in MDI with dose counter	Suspension in MDI	Suspension in MDI	Suspension in MDI
Strengths Available	108 mcg albuterol sulfate (90 mcg albuterol base) per actuation	108 mcg albuterol sulfate (90 mcg albuterol base) per actuation	108 mcg albuterol sulfate (90 mcg albuterol base) per actuation	59 mcg levalbuterol tartrate (45 mcg levalbuterol base) per actuation
Sizes Available	200 actuations and 60 actuations	200 actuations	200 actuations	200 actuations
Dose Counter	Yes	No	No	No
Indication				
Asthma	≥ 4 years of age	≥ 4 years of age	≥ 4 years of age	≥ 4 years of age
Prevention of EIB	≥ 4 years of age	≥ 4 years of age	≥ 4 years of age	Not indicated
Dosing				
Asthma	2 inhalations every 4 to 6 hours; in some patients 1 inhalation every 4 hours may be sufficient	2 inhalations every 4 to 6 hours; in some patients 1 inhalation every 4 hours may be sufficient	2 inhalations every 4 to 6 hours; in some patients 1 inhalation every 4 hours may be sufficient	2 inhalations every 4 to 6 hours; in some patients 1 inhalation every 4 hours may be sufficient
Prevention of EIB	2 inhalations 15 to 30 minutes before exercise	2 inhalations 15 to 30 minutes before exercise	2 inhalations 15 to 30 minutes before exercise	Not indicated
Overwrap Packaging	Yes; Discard the inhaler when dose counter reads 000 or 6 months after removal from the moisture-protective foil pouch, whichever comes first.	No; Discard the canister when the labeled number of actuations have been used.	No; Discard the inhaler when the labeled number of actuations have been used.	No; Discard the canister when the labeled number of actuations have been used.

HFA = hydrofluoroalkane, MDI = metered-dose inhaler, EIB = exercise-induced bronchospasm